REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

This amendment is identical in substance to the amendment filed on May 9, 2005, except that this Listing of Claims includes claims 51-54. Thus, this submission overcomes the deficiency noted in the Office Action mailed on July 21, 2005.

Claims 32-50, 55, and 56 are now pending, and claims 33-39 are withdrawn. Thus, claims 32, 40-50, 55, and 56 are pending and being examined on the merits.

I. Claim Rejections – 35 U.S.C. § 101

Claims 32, 40-50, 55, and 56 stand rejected under 35 U.S.C. § 101 because the "claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Office action at 8. Applicants respectfully traverse this ground of rejection.

The claimed invention has both well-established utility, which is specific and substantial, and specific and substantial utilities stated in the specification, as discussed below.

A. Specific and Substantial Utilities

The specification states numerous specific and substantial utilities for the claimed invention. In fact, Applicants dedicated an entire section of the specification, "VI. Applications of the Invention," to describing specific and substantial utilities of the claimed invention. Application at 20-28. For example, the specification states that the claimed invention can be used "for large scale production of a protein of interest in animals, such as in transgenic farm animals." Application at 27. In addition, the specification states that the claimed invention can be used to "create animal models of human disease." Application at 28. Thus, the specification teaches specific and substantial utilities for the claimed invention.

The Examiner concludes that the claimed invention does not have specific utility by alleging that "[t]he utility for studying transcriptional regulation is not specific to the instant invention because many other regulatory systems can serve this purpose." However, the conclusion of no utility based on the availability of other systems to study transcriptional regulation is simply a *non sequitur*. A specific and substantial utility means an "assert[ion] that the claimed invention is useful for any particular practical purpose." MPEP § 2107(II)(B)(1). It is legally irrelevant whether or not other means can be used to achieve the same utility. Thus, the existence of other regulatory systems for studying transcription regulations does not deprive the claimed invention of specific and substantial utility.

The Examiner further alleges that "the gene of interest is limited to reporter genes," but this statement is factually incorrect. The specification does not limit the gene of interest to a reporter gene. In fact, the specification broadly discloses that a whole host of genes of interest other than reporter genes can be regulated in the claimed invention. *See e.g.*, Applicants at 21.

B. Well-Established Utility

The claimed invention has a well-established utility in addition to the specific and substantial utilities disclosed in the specification. Generally, the claimed invention provides a means for controlling the expression of a gene of interest in a transgenic animal. A skilled artisan would immediately appreciate a variety of uses for such a system. For example, the ability to regulate the expression of a gene of interest, such as by selectively increasing or decreasing expression, would be recognized to have utility in a number of applications, such as *in vivo* protein production. Application at 1-2. One of skill in the art would readily recognize that certain proteins of interest, such as therapeutic proteins, are desirably transcribed at different or variable levels. The claimed invention provides a transgenic animal in which expression of a gene of interest can be controlled. Thus, a skilled artisan would immediately recognize specific and substantial utility of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

II. Claim Rejections – 35 U.S.C. § 112, first paragraph

A. Utility

Claims 32, 40-50, 55, and 56 stand rejected under 35 U.S.C. § 112, first paragraph, because the "claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Office action at 9. Applicants traverse this ground of rejection for the reasons stated above in Section I. Thus, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Enablement

Claims 32, 40-50, 55, and 56 stand rejected under 35 U.S.C. § 112, first paragraph, because the claims allegedly are not properly enabled. Applicants respectfully traverse this ground of rejection.

As discussed below, the evidence and explanation of record establishes that one of ordinary skill in the art could practice to full scope of the claimed invention using only routine experimentation.

1. Enablement does not require the transgenic animal exhibit any particular phenotype

The Examiner alleges that the "phenotype of the claimed transgenic animal is essential to enablement of the claimed invention because one skilled in the art would not know how to use a transgenic animal with claimed genotype, but shoes no phenotype." Office action at 5.

The enablement of the claimed invention should be based on the claim language and not on non-existent claim language incorrectly deemed "essential" by the Examiner. The claims state that the transcription of the gene of interest occur "**at detectable levels**." Thus, the claims do not require the transgenic animal exhibit a "phenotype," as urged by the Examiner.

One skilled in the art would know how to use the claimed transgenic animal. For example, the claimed transgenic animal that transcribes a gene of interest "at detectable levels" could be used to produce a therapeutic protein encoded by the gene of interest. Thus, enablement should be based determined without requiring the transgenic animals exhibit a "phenotype."

2. The specification provides sufficient guidance to allow a skilled artisan to make the claimed "non-human transgenic animal" without undue experimentation

The specification contains extensive guidance of how to prepare a transgene animal comprising a transgene, as claimed. For example, the specification describes extensive description of how to make and use transcriptional activator fusion proteins and how to express the fusion proteins to regulate gene expression, including how to make transgenic animals. *See e.g.*, Application at 10-16. These teachings are further validated by actual examples. Application at 28-37. Thus, the specification contains extensive guidance to allow of one of skill in the art to make the claimed invention without undue experimentation.

Indeed, the Examiner appears to agree that "the making [of] a transgenic animal following the teaching[s] of the specification is routine at the time of filing...." Office action at 6. Nonetheless, the Examiner contends that "generating any transgenic animal including lower eukaryotic organisms but also higher animal[s] such as mammal[s] with the predicted outcome of regulating gene expression in commensurate with the scope of the claim[s] is not routine experimentation based on the art recognized unpredictability." However, the prior art demonstrates that one of skill in the art could make the claimed invention without undue experimentation at the time of filing, as discussed below.

3. The state of the art at the time of invention shows that transgenic animals were produced using established methods without undue experimentation

The Examiner alleges that positional effects render the claimed invention unpredictable. However, one of skill in the art would understand the potential issues associated with positional effects and could routinely screen litters of transgenic animals to identify such issues. Thus, positional effects would not render the claimed invention

unpredictable. Instead, positional effects would be anticipated by one of skill in the art and eliminated by routinely screening transgenic animals. Such routine screening does not constitute undue experimentation, even if the screening is time consuming. *See* MPEP 2164.01.

Applicants have provided numerous references to demonstrate that making the claimed invention was routine at the time of filing. For example, Applicants previously provided the following references:

(a) Bello *et al.*, DEV. 125:2193-2202 (1998);
(b) Bieschke *et al.*, MOL. GEN. GENET. 258:571-579 (1998);
(c) Melfi *et al.*, J. MOL. BIOL. 304(5):753-763 (2001);
(d) Ridgway *et al.*, EXP. CELL RES. 256(2):392 (2000).

These references demonstrate the routine production of transgenic animals comprising gene expression systems resulting in detectable expression of a gene of interest.

The Examiner alleges that the references listed above as (a)-(d) are not sufficient to overcome the enablement rejection because the references describe only a limited number of transgenic organisms not including higher order organism, such as mammals. Office action at 6. While not acquiescing in the Examiner's reasoning, Applicants provide the following additional references further evincing enablement of the claimed invention:

(e) Schultze *et al.*, NATURE BIOTECHNOLOGY, 14(4):499-503 (1996), describes production of transgenic organisms using Tet-regulated gene expression (Exhibit A);

(f) St. Onge *et al.*, NUCLEIC ACIDS RES., 24(19):3875-77 (1996), describes production of transgenic mice, which express the Cre gene under the control of tetracycline repressor (tetR) and the acidic domain of the herpes simplex viral protein 16 (VP16) (Exhibit B);

(g) Kistner *et al.*, PROC. NAT'L ACAD. SCI., 93(20):10933-38 (1996), describes the use of tet-regulatory systems in mice (Exhibit C); and

(h) Weinmann *et al.*, PLANT J., 5(4):559-69 (1994), describes production of transgenic plants with tet-regulated genes (Exhibit D).

These references demonstrate the routine production of higher order transgenic mammalian organisms, such as mice, using systems similar to the claimed invention. Thus, these references demonstrate that making transgenic animals in general was routine at the time the application for the claimed invention was filed.

The Examiner also alleges that the references listed above as (a)-(d) are not sufficient to overcome the enablement rejection because "the cited references only demonstrate the activation of an exogenous reporter gene" and not an endogenous gene. Office action at 6. However, the Examiner provides no explanation or evidence to explain why one of skill in the art could not routinely produce transgenic animals, which contain a transgene to regulate an endogenous gene. In addition, the references of record demonstrate the expression of exogenous genes other than reporter genes (*See* Exhibit B), and Applicants attach a representative list of references demonstrating the regulation of endogenous genes (*See* Exhibit E). Thus, the references of record clearly demonstrate that one of skill in the art would be able to produce a transgenic animal, as claimed.

4. The claims are enabled

As discussed above, a skilled artisan would be able to practice the claimed invention at the time of filing without undue experimentation. Specifically, the specification provides extensive guidance of how to make the claimed invention. The references of record evince that production of transgenic animals at the time of filing required merely routine experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection against claims 32, 40-50, 55, and 56 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

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